Inactivated influenza vaccines in the elderly—are you sure?

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See *Lancet Infect Dis* 2007; **7:** 658–66

In 2005 and 2006 we published Cochrane Reviews of the effects of influenza vaccines in people aged 65 years or older,[1,2] and an overview of evidence from systematic reviews of comparative studies of all age groups.[3] The review of elderly people highlighted the thinness of the randomised evidence for this age group and the unreliable nature of evidence from cohort studies, especially large retrospective studies with data linkage. These cohorts contributed the largest proportion of evidence. We commented on the implausibility of our findings: eg, in individuals living in the community, vaccines were apparently effective for the prevention of non-specific outcomes such as death from all causes, but not for the prevention of influenza or death caused by pneumonia and influenza (figure). We concluded that the most probable explanation for such contradictory findings was selection bias, which occurred when not-so-frail elderly people were more likely to be vaccinated than their infirm peers, thus affecting the outcome.

The reviews drew much support and some scorn. Experienced researchers brushed aside the issue of study quality, stating that "observational (cohort and case-control) studies can help document reductions in attributable (not relative) risk following vaccination, and this is the information health officials need".[5] Eminent immunologists told readers that our interpretations were evidently false.[6] Some refused to acknowledge that reporting of vaccine antigenic content and its degree of match with influenza viruses circulating at the time of the study is a key variable affecting interpretation of the findings and the credibility of the study.[7] Few seemed to find strange the contradictory nature of the evidence underpinning a near-global policy for influenza immunisation, and even fewer acknowledged that the body of available evidence was methodologically weak.

Today, *The Lancet Infectious Diseases* publishes a review by Lone Simonsen and colleagues[8] of the methods used in these studies, showing that influenza vaccines cannot prevent approximately 50% of deaths from all causes, as claimed, simply because in the USA the highest estimated excess burden of mortality related to influenza is 10% per year.[8] The authors also prove that statistical methods for adjustment for residual bias used in the observational studies of influenza vaccines did not work, largely because of the difficulty of adjusting for frailty with data available in electronic records (ie, coded according to the International Classification of Diseases). Randomisation might be the only way around this systematic problem. The study further suggests that large retrospective data-linked cohort studies should no longer be done (because they are misleading), and suggest a series of five indicators for the identification of influenza-vaccine studies with a high likelihood of bias (one of them is the degree of vaccine–antigen match). Simonsen and colleagues ask again: how is it possible that no one noted the peculiar nature of the data? We would like to know too, but we

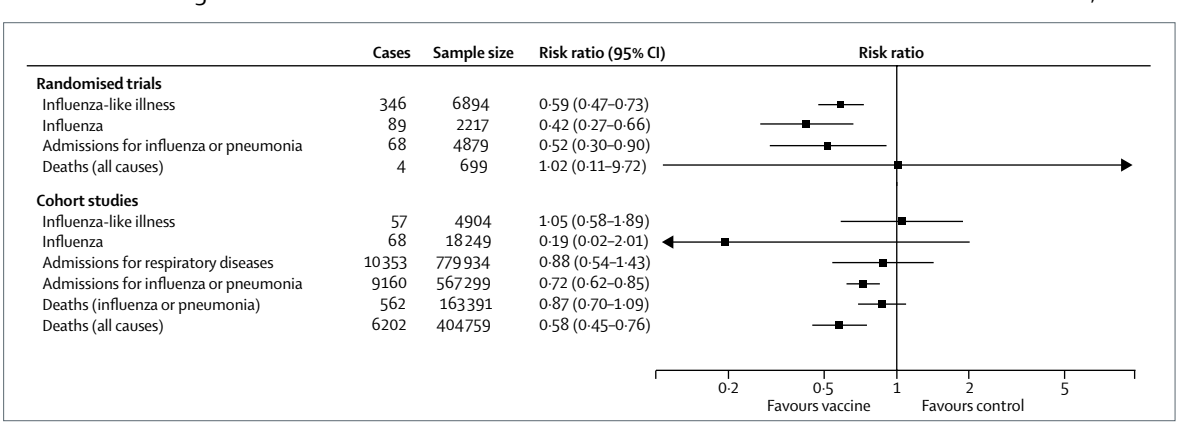

Figure: **Evidence from randomised trials of influenza vaccines versus placebo or do nothing**
Evidence from randomised trials is based on five trials with total of ten datasets. Evidence from cohort studies is based on 18 studies with total of 26 datasets.[1,2] If left-hand side of graph is covered, Forest plot seems to show good vaccine efficacy from randomised sets for more specific outcomes (such as admissions to hospital due to influenza and pneumonia) and from non-randomised studies for death from all causes. However, first observation is derived from trial of adjuvanted monovalent vaccine no longer in production. In cohort set, with indirect comparison method,[4] data show greater and significant (p=0·011) effect against deaths from all causes than for death due to influenza or pneumonia.

have shown that selection bias is only one of the many problems in reports about influenza vaccines.

If current evidence points to substantial uncertainty, what next? Simonsen and colleagues suggest that "refocusing on the likely complications of immune senescence should help clear the way for the more vigorous pursuit of other options". They also confront the ultimate taboo that drew so much scorn on the evidence overview:[9] doing randomised trials in elderly people to settle the issue conclusively. That suggestion, which seems to fly in the face of current policies, is in our opinion the only ethical and scientific way to have a definitive answer to the question of whether or not current influenza vaccines protect elderly people. However, the trials need to be large enough to detect rare outcomes, such as death due to influenza (and not from falls down stairs, poisoning, or stroke), and long enough to cover more than one influenza season because of the wide variation in viral circulation. Finally, they should be placebo-controlled, because only direct masked comparisons with an inert substance can give a reliable answer. Head-to-head comparisons with other types of influenza vaccine (which have not been assessed adequately) will not allow direct assessment of absolute vaccine effectiveness, a lesson that the pioneer designers of vaccine trials, such as Thomas Francis Jr (in the Salk poliomyelitis trial) knew only too well. Could governments be courageous and honest enough to reassess their cherished policies?

One outcome is certain. We must never again allow layers of poor research to mask substantial uncertainty about the effects of a public-health intervention and present a falsely optimistic view of policy.[10] To use Francis' words: "if one is to use public funds he must accept a responsibility to the public."[11]

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